Photoredox Catalysis

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Visible-Light-Mediated Selective Arylation of Cysteine in Batch and Flow

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Abstract: *A mild visible-light-mediated strategy for cysteine arylation is presented. The method relies on the use of eosin Y as a metal-free photocatalyst and aryldiazonium salts as arylating agents. The reaction can be significantly accelerated in a microflow reactor, whilst allowing the in situ formation of the required diazonium salts. The batch and flow protocol described herein can be applied to obtain a broad series of arylated cysteine derivatives and arylated cysteine-containing dipeptides. Moreover, the method was applied to the chemoselective arylation of a model peptide in biocompatible reaction conditions (room temperature, phosphate-buffered saline (PBS) buffer) within a short reaction time.*

The formation of C–S bonds is of high interest in the fields of organic synthesis and drug discovery.[1] However, due to the undesired coordination between metal catalysts and sulfur atoms, traditional cross-coupling methods are often inadequate strategies for C–S bond formation.[2] Despite the undesired coordination, some transition-metal-catalyzed cross-coupling methods for C–S bond formation have been reported.[3] However, these methods often rely on high reaction temperatures and/or require stoichiometric amounts of a strong base. A well-known strategy largely applied in industry for C–S bond formation is the so-called Stadler–Ziegler reaction, in which a diazonium salt reacts with an aryl thiolate to afford the desired thioether derivative.[4] Starting from the original conditions reported by Stadler and Ziegler, a plethora of methodologies have emerged, allowing milder reaction conditions.[5] Among them, our group reported a mild one-pot procedure for the synthesis of arylsulfides facilitated by photoredox catalysis.[6]

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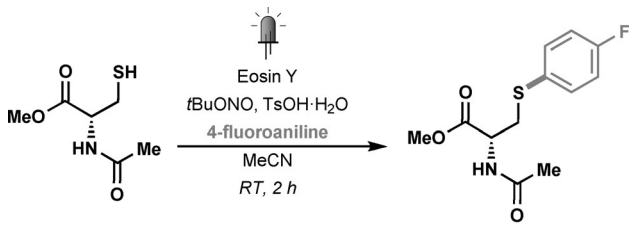
In the interest of developing mild methodologies for chemical biology purposes,[7] we envisaged modifying our procedure to achieve a visible-light-induced protocol for cysteine arylation. Specifically, we directed our attention towards the development of a biocompatible metal-free strategy involving inexpensive organic dyes as photoredox catalysts. In addition, due to the incompatibility of UV light to peptides and proteins, we reasoned that visible light photoredox catalysis would be perfectly suited to chemical biology applications owing to the milder reaction conditions (e.g. room temperature and visible light).

Novel selective chemical modifications of peptides and proteins are of pivotal importance for the study of protein–protein interactions and for the development of novel bioconjugates and drug candidates.[8] Compared to other amino acids commonly targeted for post-translational modifications, cysteine exhibits low natural abundancy and a relatively high nucleophilicity.[9] Together, these characteristics account for the generally higher selectivity and the broad reactivity profile typical for post-translational chemical modifications involving cysteine residues. Some of the most widespread strategies for cysteine bioconjugation include disulfide formation,[10] thiol–maleimide reactions,[11] and alkylation with haloalkyl reagents.[12] Other strategies use cysteine as precursor for the formation of dehydroalanine[13] (Dha), or as a handle for nucleophilic aromatic substitution allowing access to perfluorinated staples in peptides and proteins.[14] Moreover, several methodologies relying on thiol-ene[11] (or thiol-yne[15]) reactions have been reported, often requiring UV irradiation to generate the thiyl radical. Fewer records in the literature describe the use of transition metals for cysteine modification. Among them, recent developments illustrate methodologies for cysteine arylation[16] as well as viable protocols for cysteine arylation in proteins.[17] Inspired by these reports, we envisioned that photoredox catalysis could serve our purpose to obtain a mild and straightforward methodology for cysteine arylation. Moreover, we hypothesized that highly electrophilic benzenediazonium salts would be suitable as arylating agents, able to easily generate aryl radicals (E_{red} as high as 0.5 V vs. saturated calomel electrode, SCE) via a single electron transfer (SET) pathway.[18] The generated aryl radicals could then be trapped by the nucleophilic thiol moiety of cysteine.

Thus, we commenced our investigation with the arylation of *N*-Ac-L-cysteine-OMe **1a** using 4-fluorobenzenediazonium tetrafluoroborate in acetonitrile (MeCN) under batch conditions. In the absence of light and photocatalyst, a modest 26% of the desired arylated product **3g** was obtained within 2 hours reaction time (Table 1, entry 1). When exposed to

Table 1: Optimization of reaction conditions in batch for cysteine arylation.[a]



1a **3g**

Entry	Light source	Catalyst	Changes from optimized conditions	Isolated yield [%]
1	no light	none	pre-made diazonium	26
2	CFL	none	pre-made diazonium	25
3	CFL	$Ru(bpy)_3Cl_2$	pre-made diazonium	40
4	CFL	$Ru(bpy)_3Cl_2$	in situ formation, HBF_4	56
5	CFL	$Ru(bpy)_3Cl_2$	in situ formation, PTSA	59
6	**CFL**	**eosin Y**	**none**	**59**
7	CFL	eosin Y	in situ formation, 3 equiv. *t*BuONO	52[b]
8	CFL	eosin Y	DMSO	15
9	CFL	eosin Y	PBS	46
10	**white LEDs**	**eosin Y**	**continuous flow[c]**	**79 (92[b])**

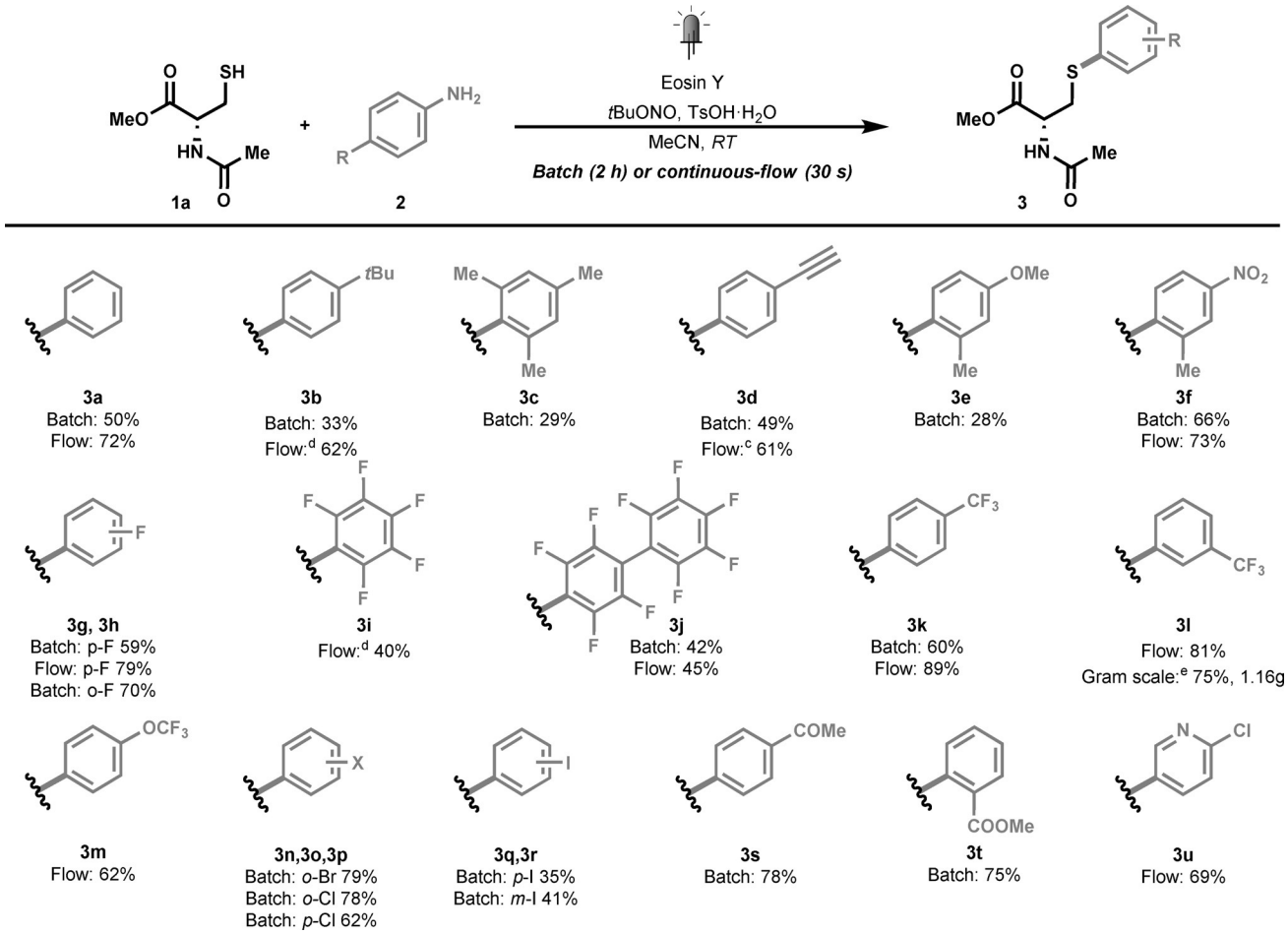
[a] Standard reaction conditions: 0.5 mmol *N*-Ac-L-cysteine-OMe (**1a**), 4-fluoroaniline (1.3 equiv), *t*-BuONO (2.0 equiv), 1.5 mol% $TsOH·H_2O$ and 1 mol% eosin Y in 5 mL MeCN (0.1 M), white CFL, 2 hours reaction time. For pre-made diazonium salts: 4-fluorobenzenediazonium tetrafluoroborate was used in absence of *t*-BuONO and $TsOH·H_2O$. [b] Yield determined by GC-MS with *n*-decane as internal standard. [c] For detailed flow conditions, see Scheme 1 and the Supporting Information.

a 24 W compact fluorescence light source (CFL), a similar yield of 25% was observed, indicating that visible light alone does not significantly increase aryl radical formation (Table 1, entry 2). However, in the presence of $Ru(bpy)_3Cl_2·6H_2O$ (1 mol%) as a benchmark photoredox catalyst, a higher yield of 40% was obtained (Table 1, entry 3). In order to minimize the risks associated with the handling of potentially explosive diazo intermediates and desiring to simplify our protocol into a one-pot procedure, we investigated the in situ formation of the diazonium salt starting from readily available 4-fluoroaniline, *tert*-butyl nitrite (*t*-BuONO, 2.0 equiv) and catalytic amounts of tetrafluoroboric acid (HBF_4, 1.5 mol%). Within 2 hours, product **3g** could be isolated in an improved 56% yield (Table 1, entry 4). Tetrafluoroborate benzenediazonium salts are easily isolated and exhibit higher stabilities as compared to diazonium salts bearing other counterions. However, by implementing the in situ formation of diazonium salts, the counterion choice appeared less restrictive (i.e. no need to use the BF_4 counter-ion to afford shelf-stable diazonium salts). Instead, we chose to use catalytic amounts of easy-to-handle *para*-toluenesulfonic acid ($TsOH·H_2O$), which gave similar results (59%, Table 1 entry 5). To develop a biocompatible strategy, we further tested the possibility to employ an organic dye, eosin Y, as photocatalyst for our transformation. Gratifyingly, in the presence of 1 mol% of eosin Y, the desired product was obtained in 59% (Table 1, entry 6). This is in line with recent reports on the ability of eosin Y to be oxidatively quenched by diazonium salts, thus generating aryl radicals.[19] Further increasing the amount of *t*-BuONO to 3 equiv did not lead to any improvement in yield (Table 1, entry 7). Solvent screening revealed that the reaction afforded lower yields in DMSO (15%, Table 1, entry 8) but proceeded well in PBS buffer (pH 8, 46% Table 1, entry 9), a commonly used solvent for peptide and protein modifications.

One of the major limitations of photocatalytic reactions conducted in batch is the inefficient irradiation of the reaction mixture, often resulting in sub-optimal yields and difficulty of scale-up.[20] In order to circumvent these issues, we translated our arylation protocol into a micro-flow procedure. We developed a photomicroreactor assembly consisting of a 3D-printed holder equipped with 0.45 mL PFA microcapillary tubing (500 μm ID) and 3.12 W white light-emitting diodes (LEDs; see the Supporting Information for microreactor details).[21] Remarkably, within only a 30 second residence time, 79% of compound **3g** was obtained (Table 1, entry 10). Due to the evolution of nitrogen gas (consistent with the reduction of diazonium salts), the formation of a slug flow was observed, which ensured optimal mixing efficiency.[22] The significant acceleration of reaction kinetics and increase in product yields can be attributed to the optimal irradiation of the reaction mixture.[20a]

With optimized conditions in hand, we evaluated the scope of our protocol both in batch and in continuous flow (Scheme 1). The arylation reaction tolerated a wide variety of substituents on the aniline coupling partner. Aniline molecules bearing alkyl substituents reacted in modest yields in batch to give the corresponding arylated cysteine derivatives (**3a** to **3c**) and improved yields were obtained in flow for compounds **3a** and **3b**. Notably, compound **3d** (49% batch vs. 61% flow) bearing an alkyne moiety could be of use for further functionalization of biomolecules through copper-catalyzed alkyne-azide cycloaddition methods (CuAAC).[23] Anilines bearing both *ortho* and *para* substituents also reacted in modest to good yields to give the desired arylated derivatives **3e** and **3f** (28% and 66% batch vs. 73% in flow for **3f**). In general, we observed that electron-deficient anilines gave higher yields as compared to the electron-rich anilines. This can be attributed to the difference in reactivity of their corresponding diazonium salts. In fact, electron-deficient aryldiazonium salts are less stable and therefore more prone to reduction via SET.[18b] Moreover, a series of fluorinated derivatives was obtained in good to excellent yields (**3g** to **3m**). Specifically, *para*- and *ortho*-fluoro (**3g** 59% batch, 82% flow, **3h** 70% batch), *para*- and *meta*-trifluoromethyl- (**3k** 60% batch, 89% flow and **3l** 81% flow) and trifluoromethoxy- (**3m** 62% flow) arylated cysteine derivatives were all prepared in good yields. Additionally, perfluoroarylated derivatives **3i** (flow 40%) and **3j** (batch 42%, flow 45%) were synthesized in satisfactory yields. Similar perfluoroarylated cysteine derivatives have been reported by Pentelute and co-workers as convenient intermediates for peptide stapling.[14a,b]

Next, we explored the potential of our methodology for Cl, Br and I-containing anilines, as all halogenated derivatives

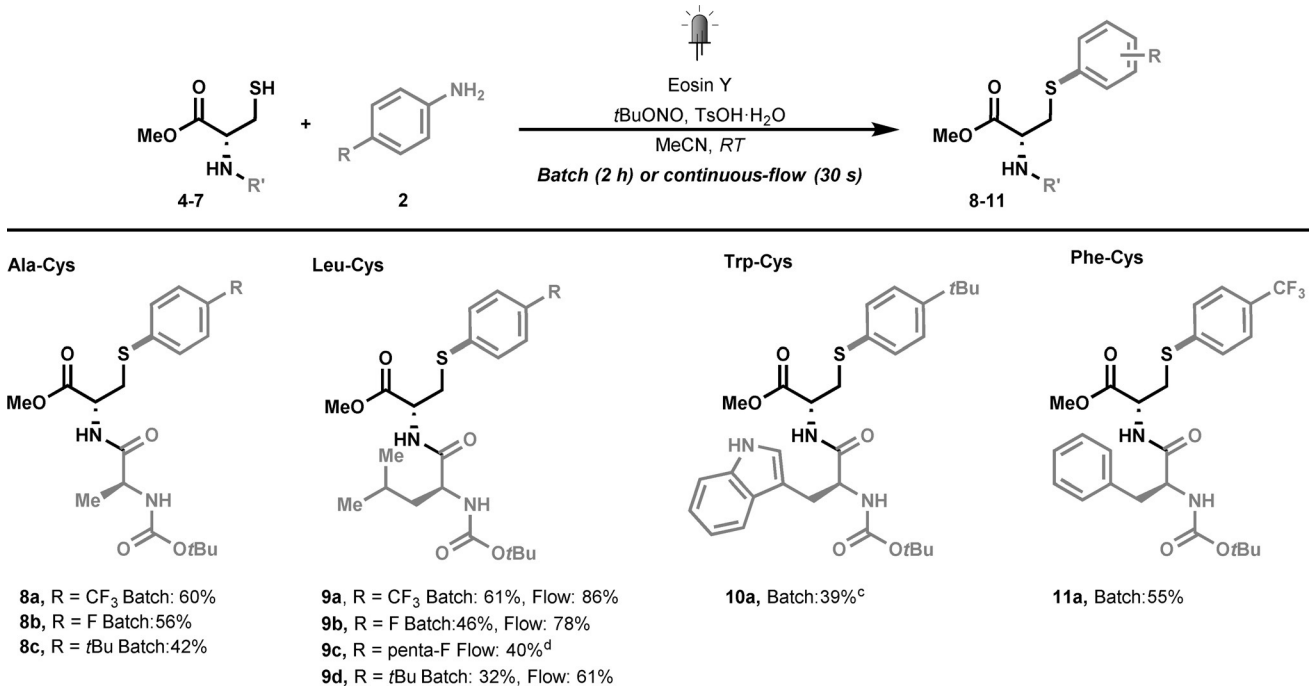


Scheme 1. Scope of cysteine arylation in batch and flow. a) Reaction conditions batch: 1.0 mmol *N*-Ac-Cys-OMe (**1a**), aniline (1.3 equiv), *t*-BuONO (2 mmol), 1.5 mol%TsOH·H_2O and 1 mol% eosin Y in 10 mL ACN (0.1 M), white CFL, 2 h reaction time. b) Reaction conditions flow: 2.0 mmol *N*-Ac-Cys-OMe (**1a**), aniline (1.3 equiv), *t*-BuONO (2 equiv), 4 mol%TsOH·H_2O and 1 mol% eosin in 40 mL ACN (0.05 M), white LED light, 30 seconds residence time; Reported yields are isolated yields [average of two runs]. c) 60 seconds residence time. d) 150 seconds residence time. e) Gram scale experiment in continuous flow (5 mmol scale).

could represent useful synthetic handles for further peptide functionalization. Both *ortho*- and *para*-Cl derivatives were obtained in satisfactory yields (**3o** 78%, **3p** 62%) as well as the *ortho*-Br derivative **3n** (79%). Moreover, *para*- and *meta*-I derivatives were synthesized (**3q** 35%, **3r** 41%) albeit in slightly diminished yields. The lower yields observed in the presence of an iodine atom could be explained by considering that iodoarene moieties are prone to iodine transfer to aryl radicals, thus affording 1,4-diiodobenzene, which we did observe as a significant side product in our reaction (detected in GC-MS).[19e] Additionally, we explored the possibility of employing keto- and ester-containing anilines, thus obtaining *para*-methyl ketone and *ortho*-methoxy ester derivatives **3s** (78%) and **3t** (75%) in good yields. Finally, we probed the reactivity of the heterocycle 3-amino-5-Cl pyridine towards our transformation. Gratifyingly, the pyridine-containing cysteine derivative **3u** was obtained in 69% yield in flow.

Owing to the ease of scalability, our flow protocol could be easily employed to obtain arylated cysteine derivatives on gram scales. Consequently, this notable feature allows one to prepare sufficient quantities for use in automated solid phase peptide synthesis (SPPS). As an example, we performed a continuous-flow scale-up experiment with *N*-Ac-L-cysteine-OMe **1a** (5 mmol) and 3-trifluoromethylaniline. Within approximately two hours of operation time, 1.16 g (72%) of derivative **3l** was obtained.

Encouraged by the results obtained for the arylation of *N*-Ac-L-Cys-OMe, we prepared a small array of cysteine-containing dipeptides to test the compatibility of our methodology with simple model peptides. Therefore, four dipeptides (**4** *N*-Boc-L-Ala-L-Cys-OMe, **5** *N*-Boc-L-Leu-L-Cys-OMe, **6** *N*-Boc-L-Trp-L-Cys-OMe and **7** *N*-Boc-L-Phe-L-Cys-OMe) were prepared in solution via native chemical ligation, and were subjected to our arylation protocol (Scheme 2).[24] Satisfyingly, *N*-Boc-L-Ala-L-Cys-OMe afforded the corresponding arylated dipeptides **8a** (60%), **8b** (56%) and **8c** (42%) in good yields. Similarly, good yields were obtained with *N*-Boc-L-Leu-L-Cys-OMe for derivatives **9a** to **9d**. A remarkable acceleration and increase in yield was observed when the arylation of *N*-Boc-L-Leu-L-Cys-OMe was conducted in flow. When attempting the arylation of *N*-Boc-L-Trp-L-Cys-OMe, we found the presence of indole to be

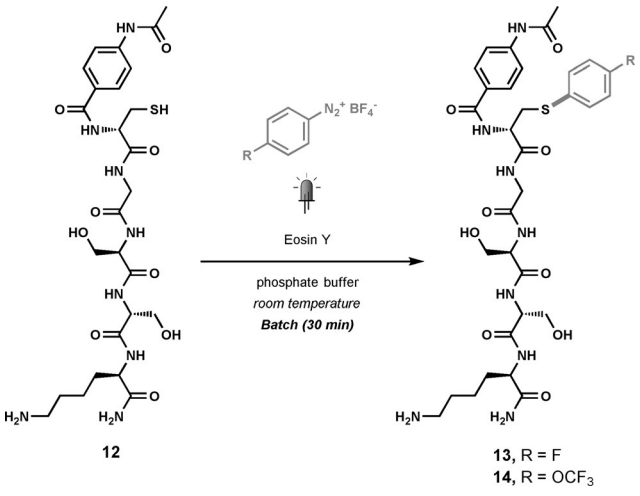


Scheme 2. Arylation of cysteine-containing dipeptides in batch and flow. a) Reaction conditions for dipeptide arylation in batch are the same as for the arylation of *N*-Ac-L-cysteine-OMe but on 0.25 mmol scale. b) Reaction conditions for dipeptide arylation in flow are the same as for the arylation of *N*-Ac-L-cysteine-OMe but on a 1 mmol scale. c) For Trp-Cys pre-made 4-*t*Bu benzenediazonium tetrafluoroborate was used. d) 150 seconds residence time.

incompatible with the in situ diazonium formation.[25] However, when pre-formed diazonium salt was added to *N*-Boc-L-Trp-L-Cys-OMe, the corresponding arylated derivative **10a** was obtained in 39% yield. Finally, *N*-Boc-L-Phe-L-Cys-OMe afforded the corresponding arylated derivative **11a** in 55% yield.

In order to further demonstrate the utility of our methodology, we focused our attention on performing our arylation strategy on more complex peptide substrates. However, we anticipated that the in situ formation of diazonium salts might be incompatible with the delicate nature of peptides and proteins. Keen to adapt our protocol to biologically relevant reaction conditions, we tested the possibility of employing pre-made diazonium salts and aqueous phosphate buffer (pH 8) for our cysteine arylation. Thus, we applied our arylation protocol under these mild reaction conditions on peptide **12**, which was used upon resin cleavage without further purification. In the presence of *para*-F benzenediazonium salt tetrafluoroborate or *para*-OCF_3 benzenediazonium tetrafluoroborate, full conversion to the desired products **13** and **14** was achieved within 30 minutes as detected by LC/MS (Scheme 3). Notably, no selectivity issues were observed in presence of lysine and serine residues, and no organic solvent was required, thus demonstrating the excellent compatibility of our protocol with other common post translational modification methods involving these residues.

In conclusion, we reported a one-pot protocol for cysteine arylation via visible light photoredox generation of aryl radicals from their corresponding diazonium salts. In situ formation of diazonium salts starting from readily available anilines reduces the risks associated with the handling of potentially explosive intermediates.[20a,22b] An array of arylated cysteine derivatives decorated with a broad range of substituents was obtained in moderate to good yields (17 examples, 28–79%). The implementation of a microflow reactor afforded faster reaction times and increased yields (30 to 150 seconds residence time, 11 examples, 45–89% yield). Moreover, a diverse set of cysteine containing dipeptides was



Scheme 3. Arylation of a cysteine-containing peptide. 1 equiv of crude peptide **12** (0.47 μmol), 10 equiv diazonium salt, 1 mol% eosin Y in 1 mL PBS buffer (pH 8), white CFL, 30 minutes reaction time.

arylated successfully in batch and in flow (12 examples, 32–86 % yield). The reaction was easily scaled-up, affording more than one gram of the arylated cysteine derivative within 2 hours of total operation time. Finally, in biologically relevant conditions, a model peptide containing additional nucleophilic side chains was selectively converted to its Cys-arylated derivative within 30 minutes. Taking into account the simplicity of our reaction conditions (atmospheric conditions, visible light irradiation, short reaction time), we believe that our procedure will be appealing to chemical biologists for post translational chemical modification of cysteine.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cysteine arylation · diazonium salts · microreactors · photochemistry · photoredox catalysis

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